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NEWS 4	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS 5	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 6	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
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NEWS 8	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data
NEWS 9	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS 10	SEP 13	FORIS renamed to SOFIS
NEWS 11	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS 12	SEP 17	CA/CAplus enhanced with printed CA page images from 1967-1998
NEWS 13	SEP 17	CAplus coverage extended to include traditional medicine patents
NEWS 14	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS 15	OCT 02	CA/CAplus enhanced with pre-1907 records from Chemisches Zentralblatt
NEWS 16	OCT 19	BEILSTEIN updated with new compounds
NEWS 17	NOV 15	Derwent Indian patent publication number format enhanced
NEWS 18	NOV 19	WPIX enhanced with XML display format
NEWS 19	NOV 30	ICSD reloaded with enhancements
NEWS 20	DEC 04	LINPADOCDB now available on STN
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NEWS 22	DEC 17	USPATOLD added to additional database clusters
NEWS 23	DEC 17	IMSDRUGCONF removed from database clusters and STN
NEWS 24	DEC 17	DGENE now includes more than 10 million sequences
NEWS 25	DEC 17	TOXCENTER enhanced with 2008 MeSH vocabulary in MEDLINE segment
NEWS 26	DEC 17	MEDLINE and LMEDLINE updated with 2008 MeSH vocabulary
NEWS 27	DEC 17	CA/CAplus enhanced with new custom IPC display formats
NEWS 28	DEC 17	STN Viewer enhanced with full-text patent content from USPATOLD
NEWS 29	JAN 02	STN pricing information for 2008 now available
NEWS 30	JAN 16	CAS patent coverage enhanced to include exemplified prophetic substances
NEWS 31	JAN 28	USPATFULL, USPAT2, and USPATOLD enhanced with new custom IPC display formats
NEWS 32	JAN 28	MARPAT searching enhanced
NEWS 33	JAN 28	USGENE now provides USPTO sequence data within 3 days of publication
NEWS 34	JAN 28	TOXCENTER enhanced with reloaded MEDLINE segment

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 NEWS 35  JAN 28  MEDLINE and LMEDLINE reloaded with enhancements

 NEWS EXPRESS  19 SEPTEMBER 2007:  CURRENT WINDOWS VERSION IS V8.2,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

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FILE 'HOME' ENTERED AT 10:32:12 ON 07 FEB 2008

=> file medline embase biosis caplus
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=> s (lhrh(w)antagonist or
luteinizing(w)hormone(w)releasing(w)hormone(w)antagonist) and 3(w)mg
L1          42 (LHRH(W) ANTAGONIST OR LUTEINIZING(W) HORMONE(W) RELEASING(W)
               HORMONE(W) ANTAGONIST) AND 3(W) MG

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2           24 DUP REM L1 (18 DUPLICATES REMOVED)

=> dis ibib abs l2 1-24

L2   ANSWER 1 OF 24  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2004:748119  CAPLUS
DOCUMENT NUMBER:         141:374832
TITLE:                   Recombinant human LH supplementation during GnRH
                         antagonist administration in IVF/ICSI cycles: a
                         prospective randomized study
AUTHOR(S):               Cedrin-Durnerin, I.; Grange-Dujardin, D.; Laffy, A.;
                         Parneix, I.; Massin, N.; Galey, J.; Theron, L.; Wolf,
                         J. P.; Conord, C.; Clement, P.; Jayot, S.; Hugues, J.
                         N.
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CORPORATE SOURCE: Centre for Reproductive Medicine, Jean Verdier Hospital, Bondy, 93143, Fr.
SOURCE: Human Reproduction (2004), 19(9), 1979-1984
CODEN: HUREEE; ISSN: 0268-1161
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB When administered in the late follicular phase to prevent an LH surge, GnRH antagonists induce a sharp decrease in serum LH levels that may be detrimental for assisted reproductive technol. cycle outcome. Therefore, a prospective study was designed to assess the effects of recombinant human (r)LH supplementation during GnRH antagonist (cetrorelix) administration. The protocol consisted of cycle programming with oral contraceptive pill, ovarian stimulation with rFSH and flexible administration of a single dose of cetrorelix (3 mg).
A total of 218 patients from three IVF centers were randomized (by sealed envelops or according to woman's birth date) to receive or not a daily injection of rLH 75 IU from GnRH antagonist initiation to hCG injection. The only significant difference was a higher serum peak E2 level in patients treated with rLH (1476 vs. 1012 pg/mL) whereas the nos. of oocytes and embryos as well as the delivery rate (25.2 vs. 24%) and the implantation rate per embryo (19.1 vs. 17.4%) were similar in both groups. These results show that in an unselected group of patients, there is no evident benefit to supplement GnRH antagonist-treated cycles with rLH.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:214872 CAPLUS
DOCUMENT NUMBER: 142:349212
TITLE: Premenstrual administration of gonadotropin-releasing hormone antagonist coordinates early antral follicle sizes and sets up the basis for an innovative concept of controlled ovarian hyperstimulation
AUTHOR(S): Fanchin, Renato; Branco, Altina Castelo; Kadoch, Isaac Jacques; Hosny, Ghada; Bagirova, Mira; Frydman, Rene
CORPORATE SOURCE: Department of Obstetrics and Gynecology and Reproductive Medicine, Hopital Antoine Beclere, Clamart, Fr.
SOURCE: Fertility and Sterility (2004), 81(6), 1554-1559
CODEN: FESTAS; ISSN: 0015-0282
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: To investigate whether premenstrual administration of a GnRH antagonist coordinates early antral follicle sizes during the subsequent follicular phase. Design: Prospective, longitudinal study. Setting: University Hospital in France Patient(s): Twenty-five women, 50 cycles. Intervention(s): On cycle day 2 (control/day 2), women underwent measurements of early antral follicles by ultrasound and serum FSH and ovarian hormones. On day 25, they received a single cetrorelix acetate administration, 3 mg. On the subsequent day 2 (premenstrual GnRH antagonist/day 2), participants were re-evaluated as on control/day 2. Main Outcome Measure(s): Magnitude of follicular size discrepancies. Result(s): Follicular diams. (4.1 vs. 5.5 mm) and follicle-to-follicle size differences decreased on premenstrual GnRH antagonist/day 2 as compared with control/day 2. Consistently, FSH (4.5 vs. 6.7 mIU/mL), estradiol (E2) (23 vs. 46 pg/mL), and inhibin B (52 vs. 76 pg/mL) were lower on GnRH antagonist/day 2 than on control/day 2. Conclusion(s): Premenstrual GnRH antagonist administration reduces diams. and size disparities of early antral follicles on day 2, likely through the prevention of luteal FSH elevation and early follicular development.

This simple, original approach may be used to coordinate multifollicular development in controlled ovarian hyperstimulation.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 24 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004065551 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14767559
TITLE: Luteinizing hormone-releasing hormone antagonist Cetrorelix regulates the expression of Galphas and Galphai protein subunits and adenylate cyclase activity in rat ovary, breast and pituitary.
AUTHOR: Collado Beatriz; Carmena Maria J; Cortes Joaquin; Schally Andrew V; Prieto Juan C
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Alcala, Spain.
SOURCE: International journal of oncology, (2004 Mar) Vol. 24, No. 3, pp. 725-30.
Journal code: 9306042. ISSN: 1019-6439.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200410
ENTRY DATE: Entered STN: 10 Feb 2004
Last Updated on STN: 26 Oct 2004
Entered Medline: 25 Oct 2004
AB The mechanisms by which luteinizing hormone-releasing hormone (LH-RH) antagonists act on extra-pituitary tissues are poorly understood. In view of extensive use of Cetrorelix in gynecology and oncology, we investigated its effects on signal transduction pathways of G-protein coupled receptors and adenylate cyclase which are involved in a huge array of cellular events including normal and pathological cell proliferation. Thirty days after a single i.m. injection of 3 mg Cetrorelix pamoate depot to female rats, normal or ovariectomized, we evaluated the effects of this chronic treatment on the expression of alphas and alphai G-protein subunits in the ovary, breast and pituitary, as well as the adenylate cyclase response in vitro to LH-RH, vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP). Varied patterns of response to Cetrorelix, depending on the gland and estrogenic status were observed. Western blot analysis showed a modest decrease of alphas and a modest increase of alphai G-protein subunit levels in ovary, a marked increase of alphas and alphai levels in breast, and a lack of effect on alphas/alphai levels in pituitary. In the ovary, adenylate cyclase activity was not changed by in vitro addition of LH-RH, but the responses to VIP and PACAP increased after Cetrorelix treatment. In the breast, chronic administration of the LH-RH antagonist decreased the adenylate cyclase response to PACAP, which returned to normal after ovariectomy. In the pituitary, Cetrorelix abolished the stimulatory effect of VIP upon adenylate cyclase activity. Thus, the LH-RH antagonist Cetrorelix exerted selective modifications at different steps of the G-protein coupled receptors/adenylate cyclase system of signal transduction in the rat ovary, breast and pituitary.

L2 ANSWER 4 OF 24 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002259522 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11998957
TITLE: Plasma and follicular fluid concentrations of LHRH antagonist cetrorelix (Cetrotide) in controlled ovarian stimulation for IVF.

AUTHOR: Ludwig M; Albano C; Olivennes F; Felberbaum R E; Smitz J; Ortmann O; Romeis P; Niebch G; Pechstein B; Riethmuller-Winzen H; Devroey P; Diedrich K
CORPORATE SOURCE: Department of Gynecology and Obstetrics, Medical University of Lubeck, Germany.. Ludwig_M@t-online.de
SOURCE: Archives of gynecology and obstetrics, (2002 Jan) Vol. 266, No. 1, pp. 12-7.
Journal code: 8710213. ISSN: 0932-0067.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 10 May 2002
Last Updated on STN: 8 Oct 2002
Entered Medline: 4 Oct 2002

AB Cetrorelix was administered in differing daily dosages for controlled ovarian stimulation. The dosage levels were 3 mg (9 cycles), 1 mg (19 cycles), 0.5 mg (43 cycles), 0.25 mg (46 cycles) and 0.1 mg (7 cycles). In the 3 mg, 1 mg and 0.5 mg group the respective median plasma concentrations of cetrorelix on the day of oocyte pick-up (OPU) were 2.10 ng/ml, 1.42 ng/ml and 0.88 ng/ml and 1.03 ng/ml, 0.46 ng/ml and 0.49 ng/ml on the day of embryo transfer (ET). In the 0.25 mg and 0.1 mg groups plasma cetrorelix levels were below the limit of quantification. The cetrorelix concentrations in follicular fluid (FF) in the 0.25 mg group were detectable in only 14 out of 44 samples, while in the 0.1 mg group no detectable concentrations could be obtained. We also examined 80 cycles after single doses of 5 mg (7 cycles), 3 mg (42 cycles), and 2 mg (31 cycles) cetrorelix. On the day of OPU the respective median plasma concentrations of cetrorelix were 0.57 ng/ml, 0.62 ng/ml, and 0.56 ng/ml, and 0.61 ng/ml and 0.28 ng/ml on the day of ET in the 5 mg and 3 mg groups. In the 2 mg group, the plasma concentrations fell to below limits of quantification in 8/9 samples on the day of ET. In 26 out of 27 FF samples cetrorelix was detectable in the 3 mg single dose group (median level: 0.69 ng/ml).

L2 ANSWER 5 OF 24 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2000329049 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10872648
TITLE: Pituitary and gonadal endocrine effects and pharmacokinetics of the novel luteinizing hormone-releasing hormone antagonist teverelix in healthy men--a first-dose-in-humans study.
AUTHOR: Erb K; Pechstein B; Schueler A; Engel J; Hermann R
CORPORATE SOURCE: Department of Human Pharmacology, Corporate Research, ASTA Medica AG, Frankfurt am Main, Germany.. KatharinaErb@t-online.de
SOURCE: Clinical pharmacology and therapeutics, (2000 Jun) Vol. 67, No. 6, pp. 660-9.
Journal code: 0372741. ISSN: 0009-9236.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 14 Jul 2000
Last Updated on STN: 14 Jul 2000

Entered Medline: 6 Jul 2000

AB BACKGROUND. Teverelix is a novel synthetic peptidic luteinizing hormone-releasing hormone (LHRH) antagonist. METHODS: Single subcutaneous morning doses of teverelix acetate (either 0.5, 1, 2, 3, or 5 mg base) were investigated in a randomized, single-blind, placebo-controlled, dose-escalating parallel-group design in healthy men. Six subjects received teverelix, and two subjects received placebo per dose level. Blood samples for lutropin, luteinizing hormone (LH), and follitropin, follicle-stimulating hormone (FSH), and testosterone, as well as for pharmacokinetics, were withdrawn up to 120 hours after dosing. Serum hormone levels were determined by electrochemicoluminescence immunoassays, and plasma teverelix concentrations were determined by radioimmunoassay. RESULTS: Teverelix led to a rapid, marked suppression of LH, testosterone and, to a lesser extent, FSH. Median maximum suppressions compared with predose levels were -93% for LH and -54% for FSH after teverelix 5 mg, and -93% for testosterone after teverelix 3 mg, respectively. After 5 mg teverelix, testosterone suppression <1 ng/mL started a median of 12 hours after dosing and lasted for a median of 33 hours. The duration of testosterone suppression increased with dose. Geometric means of peak teverilix plasma concentrations were 4.5 ng/mL (0.5 mg teverelix) to 49.0 ng/mL (5 mg teverelix) and tmax occurred between 1 and 4 hours after dosing. Geometric means of the area under the teverelix plasma concentration-time course from zero to time of the last quantifiable plasma concentration [AUC(O-tlast)] were 54.9 ng x h/mL (0.5 mg teverelix) to 881.8 ng x h/mL (5 mg teverelix). Median values for apparent terminal half-lives ranged from 24 to 75 hours. The most frequently reported adverse events were short-lasting mild injection-site reactions. CONCLUSIONS: Teverelix showed pronounced LH and testosterone suppressive effects after single subcutaneous doses in healthy men. Duration of hormone suppression increased with dose. Teverelix was well tolerated. This profile indicates potential for further clinical use.

L2 ANSWER 6 OF 24 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:131344 BIOSIS

DOCUMENT NUMBER: PREV200000131344

TITLE: Prospective, randomized, controlled study of in vitro fertilization-embryo transfer with a single dose of a luteinizing hormone-releasing hormone (LH-RH) antagonist (cetrorelix) or a depot formula of an LH-RH agonist (triptorelin).

AUTHOR(S): Olivennes, Francois [Reprint author]; Belaisch-Allart, Joelle; Emperaire, Jean-Claude; Dechaud, Herve; Alvarez, Sylvia; Moreau, Laurence; Nicollet, Bernard; Zorn, Jean-Rene; Bouchard, Philippe; Frydman, Rene

CORPORATE SOURCE: Service de Gynecologie-Obstetrique, Hopital A. Beclere, 157, Rue de la Porte De Trivaux, 92140, Clamart Cedex, France

SOURCE: Fertility and Sterility, (Feb., 2000) Vol. 73, No. 2, pp. 314-320. print.
CODEN: FESTAS. ISSN: 0015-0282.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 12 Apr 2000
Last Updated on STN: 4 Jan 2002

AB Objective: To confirm the value of a single dose of 3 mg of cetrorelix in preventing the occurrence of premature LH surges. Design: Multicenter randomized, prospective study. Setting: Reproductive medicine units. Patient(s): Infertile patients undergoing ovarian stimulation for IVF-ET. Intervention(s): A single dose of 3 mg of cetrorelix (Cetrotide; ASTA Medica, Frankfurt, Germany) (115 patients) was administered in the late follicular phase. A depot

preparation of triptorelin (Decapeptyl; Ipsen-Biotech, Paris, France) was chosen as a control agent (39 patients). Ovarian stimulation was conducted with hMG (Menogon; Ferring, Kiel, Germany). Main Outcome Measure(s): Premature LH surges (LH level >10 IU/L), progesterone level greater than 1 ng/L, and IVF results. Result(s): No LH surge occurred after cetrorelix administration. The patients in the cetrorelix group had a lower number of oocytes and embryos. The percentage of mature oocytes and fertilization rates were similar in both groups, and the pregnancy rates were not statistically different. The length of stimulation, number of hMG ampules administered, and occurrence of the ovarian hyperstimulation syndrome were lower in the cetrorelix group. Tolerance of cetrorelix was excellent. Conclusion(s): A cetrorelix single-dose protocol prevented LH surges in all patients studied. It compares favorably to the "long protocol" and could be a protocol of choice in IVF-ET.

L2 ANSWER 7 OF 24 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:174017 BIOSIS
DOCUMENT NUMBER: PREV200000174017
TITLE: Pharmacokinetic-pharmacodynamic modeling of testosterone and luteinizing hormone suppression by cetrorelix in healthy volunteers.
AUTHOR(S): Pechstein, Birgit [Reprint author]; Nagaraja, Nelamangala V.; Hermann, Robert; Romeis, Peter; Locher, Mathias; Derendorf, Hartmut
CORPORATE SOURCE: ASTA Medica AG, Weismuellerstr. 45, 60314, Frankfurt am Main, Germany
SOURCE: Journal of Clinical Pharmacology, (March, 2000) Vol. 40, No. 3, pp. 266-274. print.
CODEN: JCPCBR. ISSN: 0091-2700.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 3 May 2000
Last Updated on STN: 4 Jan 2002

AB Cetrorelix (CET), a potent luteinizing hormone-releasing hormone (LH-RH) antagonist, was recently approved for the prevention of premature ovulation in patients undergoing a controlled ovarian stimulation (COS), followed by oocyte pickup and assisted reproductive techniques (ART), and is currently under clinical trials for benign prostate hyperplasia, endometriosis, and tumors sensitive to sex hormones. CET suppresses luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone (T) in men. The purpose of this study was to evaluate the pharmacokinetics and absolute bioavailability of 3 mg intravenously and subcutaneously administered CET in healthy male and female volunteers and to develop a pharmacokinetic-pharmacodynamic (PK-PD) model to link the plasma concentrations of CET to the T and LH suppression in males. Following intravenous (IV) (n = 5) and subcutaneous (SC) (n = 6) administration of CET acetate, CET and hormone plasma levels were measured by radioimmunoassay (RIA) and enzyme immunoassay (EIA) methods, respectively. Pharmacokinetics of CET was explained by a three-compartment model for the IV route and by a two-compartment model with first-order absorption for the SC route. Average absolute bioavailability after SC administration was 85%. There were no differences in the pharmacokinetics between male and female subjects (ANOVA, $p > 0.05$). Single IV and SC doses of CET caused immediate and distinct suppression of LH, FSH, and T levels by 80%, 45%, and 95% of their baseline levels, respectively. The duration of hormone suppression was longer for the SC route. An indirect-response PK-PD Emax model was developed to link the measured CET plasma concentrations with the respective T or LH levels. In addition, the circadian rhythm of T levels was accounted by including a cosine function in a second separate PD model. The PD model with cosine function was applied to T baseline levels

as well as to the suppressed concentrations after CET dosing. The two models adequately described the PK-PD relationship between plasma levels of CET and T suppression following IV and SC dosing. The EC50 values (mean +- SD) for the suppression of T were similar ($p > 0.05$) between the two routes of administration and the two models.

L2 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2000:459854 CAPLUS
DOCUMENT NUMBER: 133:305174
TITLE: Cetrorelix, ASTA Medica AG
AUTHOR(S): Norman, Peter
CORPORATE SOURCE: Norman Consulting, Burnham, Bucks, SL1 8JW, UK
SOURCE: Current Opinion in Oncologic, Endocrine & Metabolic Investigational Drugs (2000), 2(2), 227-248
CODEN: COODF2; ISSN: 1464-8466
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 221 refs. ASTA Medica has developed cetrorelix, an injectable LHRH antagonist for the treatment of sex hormone-dependent disorders such as breast, ovarian and prostate cancers, benign prostate hyperplasia and gynecol. disorders including uterine myoma and endometriosis. Cetrorelix has been launched for the treatment of infertility in Germany, Sweden, Netherlands, Austria and Belgium. The compound is in phase II trials for prostate cancer, benign prostatic hyperplasia and uterus myomatosus. In May 1999, cetrorelix was launched for the treatment of infertility in Germany and the UK, with subsequent launches in Sweden, The Netherlands, Austria and Belgium. In Nov. 1998, the company reported that cetrorelix was undergoing registration for the controlled induction of ovulation and on 13 Apr. 1999, it was approved by the European Commission for marketing in the 15 countries of the EU for the treatment of infertility. ASTA Medica and Ares-Serono intended to file a US NDA submission for cetrorelix in fertility treatment by the end of 1999. Two cetrorelix dosage regimens have been confirmed by EU regulators to avoid LH surge, (i) 0.25 mg powder and solvent solution for injection starting on days 5-6 of follicular stimulation; or (ii), 3 mg cetrorelix as a single dose given on the seventh day of follicular stimulation. The compound is in phase II trials for prostate cancer, benign prostatic hyperplasia and uterus myomatosus. In all three conditions initial reports indicate that 1-2-mo treatment with cetrorelix provides rapid, symptomatic relief. ASTA Medica has formed a joint venture company, Kayaku ASTA Medica Co Ltd, with Nippon Kayaku for joint development of cetrorelix. Cetrorelix is licensed to Shionogi in Japan, where it is in phase II trials. ASTA holds a patent, WO-09500168, for the use of cetrorelix in the treatment of AIDS and AIDS-related disease.
REFERENCE COUNT: 221 THERE ARE 221 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:740190 CAPLUS
DOCUMENT NUMBER: 132:102992
TITLE: Ovarian stimulation for in-vitro fertilization/intracytoplasmic sperm injection with gonadotrophins and gonadotrophin-releasing hormone analogues: agonists and antagonists
AUTHOR(S): Felberbaum, R.; Diedrich, K.
CORPORATE SOURCE: Department of Obstetrics and Gynecology, The Medical University of Lubeck, Lubeck, 23538, Germany
SOURCE: Human Reproduction (1999), 14(Suppl. 1), 207-221
CODEN: HUREEE; ISSN: 0268-1161

PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The gonadotropin-releasing hormone (GnRH) antagonists Cetrorelix and Ganirelix have been used in recent years in clin. studies to prove that these compds. reliably prevent the onset of premature LH surges during ovarian stimulation. Cetrorelix has been applied in single and multiple dose protocols, while Ganirelix has until now only been used in the multiple dose protocol. In the latter protocol, ovarian stimulation is started on day 2 or 3 of the spontaneous cycle with human menopausal gonadotropin or recombinant FSH. Daily administration of the GnRH antagonist at its min. ED (0.25 mg/day s.c.) occurs from the sixth day of stimulation onwards until ovulation induction by human chorionic gonadotropin. In the single dose protocol, 3 mg of the GnRH antagonist Cetrorelix was injected on day 8 of the stimulation cycle. Both protocols have been proven to be safe and effective. Fertilization rates of >60% in in-vitro fertilization and >70% in intracytoplasmic sperm injection, as well as clin. pregnancy rates of .apprx.30% per transfer, sound most promising. The incidence of a premature LH surge is below 2%. The incidence of severe ovarian hyperstimulation syndrome seems to be lower under antagonist treatment than in the long agonistic protocol. Treatment time is significantly shortened.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 24 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 97200805 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9048634
TITLE: Immunohistochemical analysis of androgen effects on androgen receptor expression in developing Leydig and Sertoli cells.
AUTHOR: Shan L X; Bardin C W; Hardy M P
CORPORATE SOURCE: Center for Biomedical Research, Population Council, New York, New York 10021, USA.
CONTRACT NUMBER: R29 HD-32588 (United States NICHD)
SOURCE: Endocrinology, (1997 Mar) Vol. 138, No. 3, pp. 1259-66. Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 22 Apr 1997
Last Updated on STN: 22 Apr 1997
Entered Medline: 7 Apr 1997
AB Leydig and Sertoli cells are both targets of androgen action in the testis. Androgen exerts contrasting effects on the two cell types partially inhibiting steroidogenesis in adult Leydig cell and stimulating adult Sertoli cell functions required to support spermatogenesis. The developmental changes in the messenger RNA (mRNA) levels of androgen receptor (AR) also differ between Leydig and Sertoli cells, with Leydig cell AR mRNA being highest on day 35 postpartum, whereas Sertoli cell AR mRNA levels are highest on day 90. The purpose of the present study was to determine if the concentrations of AR in Leydig and Sertoli cells are differentially regulated during development using quantitative immunostaining. AR protein levels were measured in rat testes after hormonal treatments at three developmental stages: on days 21, 35, and 90 postpartum. At each age, five groups of animals were treated for 4 days with: 1) vehicle; 2) LHRH antagonist (NalGlu, 0.

3 mg/kg BW.day) to suppress endogenous levels of androgen that accompany inhibition of LH and FSH secretion; 3) NalGlu + LH (0.2 mg/kg BW.day); 4) NalGlu + testosterone (T, at 7.5 mg/kg BW.day); and 5) NalGlu + MENT (a potent synthetic androgen, 7 alpha-methyl-19-nortestosterone, 0.7 mg/kg BW.day). AR protein was visualized by immunohistochemistry and measured by computer-assisted image analysis in Leydig and Sertoli cells using frozen sections of tests. After NalGlu treatment, AR levels in Leydig cells declined sharply to 42% and 31% of vehicle control ($P < 0.01$) in the 21 and 35 days postpartum age groups, respectively, but in 90-day-old rats there was no change. AR levels were partially maintained by exogenous LH, and completely maintained by exogenous androgen treatments in Leydig cells from 21- and 35-day-old rats, whereas in Leydig cells from 90-day-old rats, AR levels were unaffected in all treatment groups. In contrast, after NalGlu treatment, the AR concentration in Sertoli cells from 90-day-old rats were reduced to 32% of control ($P < 0.01$). Moreover, in Sertoli cells from 90-day-old rats, AR levels were partially maintained by LH and completely maintained by androgens. A similar trend was observed on day 35. On day 21, however, AR levels in immature Sertoli cells were unaffected in all treatment groups. These results indicate that androgen maximally stimulates AR levels in immature Leydig cells but is without significant effect in adult Leydig cells. In contrast, AR levels in Sertoli cells are more sensitive to androgen regulation in adult compared with immature animals. These findings indicate that there are distinct mechanisms controlling AR concentrations in Leydig and Sertoli cells during the development of the testis.

L2 ANSWER 11 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:511666 CAPLUS
DOCUMENT NUMBER: 129:255149
TITLE: Multiple dose protocol for the administration of GnRH-antagonists in IVF: the "Lubeck-protocol"
AUTHOR(S): Felberbaum, R.; Diedrich, K.
CORPORATE SOURCE: Department of Obsterics and Gynecology, Medical University of Lubeck (D), Germany
SOURCE: In Vitro Fertilization and Assisted Reproduction, Proceedings of the World Congress of in Vitro Fertilization and Assisted Reproduction, Vancouver, B. C., May 24-28, 1997 (1997), 397-404. Editor(s): Gomel, Victor; Leung, Peter C. K. Monduzzi Editore: Bologna, Italy.
CODEN: 66MRAP
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Due to their different pharmacol. mode of action GnRH-antagonists are able to suppress serum-concns. of LH within hours. Instead of "down-regulation" and "desensitization" a classic competitive blockage of the GnRH-receptors on the cell-membrane of the gonadotrophic cells seems to take place. The "flare up", typical for agonistic GnRH-analogs is completely avoided. While the first generation of GnRH-antagonists caused important problems due to allergic reactions, which inhibited their clin. introduction, Cetrorelix and Ganirelix as representatives of the youngest generation of these compds. seem to avoid these disturbances completely. Cetrorelix was introduced first in our IVF-program to scrutinize the possibility of avoiding premature LH-surges. All patients were treated with human menopausal gonadotropin (HMG), starting on day 2. From day 7 until induction of ovulation by human chorionic gonadotropin (HCG) Cetrorelix is administered s.c. in a daily fashion. Starting with a dosage of 3-mg Cetrorelix/day no premature LH-surges could be observed Also, 1 mg/day, 0.5 mg/day and 0.25 mg/day administered according to the described "Lubeck-protocol" avoided any premature LH-surges. The mean courses of FSH and LH in the different dosage groups

were quite similar with a profound suppression of LH. Estradiol concns. reflected a satisfactory follicular development. The fertilization-rate after IVF in cases of tubal infertility or ICSI in cases of male subfertility were within the range to be expected after normal oocyte maturation.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:249914 CAPLUS
DOCUMENT NUMBER: 124:279399
TITLE: A new method for controlling the precise time of occurrence of the preovulatory gonadotropin surge in superovulated goats
AUTHOR(S): Baril, G.; Pougnard, J. L.; Freitas, V. J. F.; Leboeuf, B.; Saumande, J.
CORPORATE SOURCE: Station de Physiologie de la Reproduction des Mammiferes Domestiques, Institut National de la Recherche Agronomique, Nouzilly, 37380, Fr.
SOURCE: Theriogenology (1996), 45(3), 697-706
CODEN: THGNBO; ISSN: 0093-691X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In goats treated to induce superovulation, insemination at a predetd. time after the end of progestagen treatment leads to a low fertilization rate. To solve this problem we developed a new treatment based on the control of the occurrence of the endogenous LH peak with a GnRH antagonist (Antarelix). The first experiment was designed to determine the dose of LH required to mimic a spontaneous LH preovulatory discharge; the injection of 3 mg, i.v. of pLH induced a peak of the same amplitude and duration as the spontaneous peak. Subsequently, in the second experiment, we compared 2 doses of Antarelix (0.5 and 1 mg, s.c.) administered 12 h after sponge removal (9 goats/treatment group). The dose of 0.5 mg was selected for further expts. because it was effective in the inhibition of the endogenous LH peak and had no detrimental effect on the quality of embryos. In the final experiment, 48 goats received the new treatment and were inseminated (intrauterine) only once 16 h after LH injection; 41 were flushed and produced 5.3 (m) transferable embryos. The developmental stage and the number of cells/embryo were within the range that has been reported for embryos produced with conventional treatments. In conclusion, with the described method, it is possible to inseminate goats at a predetd. time without decreasing the number of transferable embryos. This technique will encourage the development of embryo transfer within genetic programs, and it will be a valuable tool for the production of zygotes for gene transfer.

L2 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1995:387266 CAPLUS
DOCUMENT NUMBER: 122:205558
TITLE: A-75998: a fourth generation GnRH antagonist: II. Preclinical studies in female primates
AUTHOR(S): Gordon, Keith; Williams, Robert F.; Greer, Johnathan; Bush, Eugene N.; Haviv, Fortuna; Herrin, Marley; Hodgen, Gary D.
CORPORATE SOURCE: Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, Norfolk, VA, 23507, USA
SOURCE: Endocrine (1994), 2(12), 1141-4
CODEN: EOCRE5; ISSN: 1355-008X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A-75998 is a newly developed GnRH antagonist combining high potency, low histamine release potential and high aqueous solubility Here, we report the results of preclin. investigations in ovariectomized (OVX) and intact eugonadal female monkeys. In study I, we characterized the effects of a single s.c. administration of 0.3 mg/kg A-75998 (in saline vehicle) on serum LH and FSH levels in OVX monkeys. Significant suppression of serum LH levels was evident within 1 to 2 h, reaching a nadir by 24 h and remaining suppressed for 5 to 6 days before slowly recovering to pretreatment levels within 2 to 4 wk. In study II, we administered 0.1 mg/kg A-75998 (in saline vehicle) s.c. to intact female monkeys on menstrual cycle day 2. Significant suppression of serum estradiol (E2) levels was evident by 24 h and lasted 3 to 5 days. In study III, we administered A-75998 to intact female monkeys i.v. via Alza osmotic minipumps at doses of 0.025 and 0.05 mg/kg/day for 7 days beginning on menstrual cycle day 2. Serum E2 levels were suppressed below 30 pg/mL in all six monkeys while the pumps were operative, with recovery evident 3 to 4 days after pump removal. These results demonstrate that the GnRH antagonist A-75998 produces profound and prompt suppression of serum LH and FSH in OVX monkeys at a dose of 0.3 mg /kg, and produces suppression of serum estradiol levels in intact female monkeys at doses as low as 0.025 mg/kg/day. This is one-quarter of the daily dose needed to suppress serum testosterone levels in male monkeys, thus illustrating a marked gender difference in sensitivity to GnRH antagonists. Whether this gender difference is due to differential pituitary or gonadal sensitivities remains to be determined

L2 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1995:387265 CAPLUS
DOCUMENT NUMBER: 122:205557
TITLE: A-75998: a fourth generation GnRH antagonist: I. Preclinical studies in male primates
AUTHOR(S): Gordon, Keith; Williams, Robert F.; Greer, Jonathan; Bush, Eugene N.; Haviv, Fortuna; Herrin, Marley; Hodgen, Gary D.
CORPORATE SOURCE: Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, Norfolk, VA, 23507, USA
SOURCE: Endocrine (1994), 2(12), 1133-9
CODEN: EOCRE5; ISSN: 1355-008X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A-75998 is a fourth generation GnRHant. Here, we report the results of preclin. investigations in intact adult male cynomolgus monkeys. In study I, daily s.c. administration of 0.1 mg/kg/day A-75998 in saline for 10 days suppressed serum levels of testosterone (T) to less than 0.5 ng/mL within 4 days and maintained suppression until 3 to 4 days after cessation of treatment when a marked rebound effect was seen. In study II, daily s.c. administration of 0.03 mg/kg/day for 30 days was ineffective in producing suppression of serum T levels. Rather, an apparent pseudo-stimulatory effect on serum T levels was seen with this dose regimen. Both 0.1 and 0.3 mg/kg/day were fully effective in producing, and maintaining full suppression of serum T levels for the 30 day duration of treatment. In study III, A-75998 was administered as a slow i.v. (jugular) infusion via Alzet osmotic minipumps. Levels of T in the three monkeys receiving 0.03 mg/kg/day were not fully suppressed, whereas T levels of all monkeys receiving either 0.1 and 0.2 mg/kg/day were fully suppressed for the 7 days the pumps were present. In study IV, we re-examined the apparent stimulatory effects of daily s.c. administration of 0.03 mg/kg/day A-75998. We found that administration of 0.03 mg/kg s.c. resulted in an initial decline in serum T levels, reaching a nadir by 12 h followed by a return to pretreatment values (or above) by 24 h. We conclude that A-75998 is capable of producing full suppression of serum T levels in adult male monkeys when

administered either as daily s.c. injections or as a slow i.v. infusion via Alzet osmotic minipumps.

L2 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1995:452610 CAPLUS
DOCUMENT NUMBER: 122:205577
TITLE: In vivo effects of a potent GnRH antagonist ORG 30850: physiologic evidence that down-regulation of GnRH receptors does not occur
AUTHOR(S): Gordon, Keith; Scott, Richard T.; Williams, Robert F.; Danforth, Douglas R.; Loozen, Hubert J. J.; Kloosterboer, Helenius J.; Hodgen, Gary D.
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, VA, USA
SOURCE: Journal of the Society for Gynecologic Investigation (1994), 1(4), 290-6
CODEN: JSGIED; ISSN: 1071-5576
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Our purpose was to determine the pituitary responsiveness to exogenous GnRH in GnRH antagonist-suppressed ovariectomized monkeys. This was a prospective exptl. non-human primate study performed at the research labs. of The Jones Institute for Reproductive Medicine. Seventeen long-term ovariectomized cynomolgus monkeys were studied. The GnRH antagonist ORG 30850 was administered to long-term ovariectomized monkeys assigned to one of six groups: single s.c. injections in group A, 0.3 mg /kg; group B, 1.0 mg/kg; and group C, 3.0 mg/kg; and six consecutive daily s.c. injections in group D, 0.3 mg/kg; group E, 1.0 mg/kg; and group F, 3.0 mg/kg. Blood samples were collected daily from 10 days before treatment until 22 days after treatment, then weekly for 6 addnl. weeks. I.v. GnRH stimulation tests (10 μg/kg) were performed on the day after vehicle injection (control) and the day after completion of treatment(s), and then at weekly intervals. The main outcome measures were serum levels of LH, FSH, and ORG 30850. Administration of ORG 30850 resulted in suppression of LH and FSH in all treatment groups. Long-term suppression (greater than 2 wk) was evident in all primates receiving a cumulative dose of at least 1 mg/kg. Paradoxically, the responsiveness of the pituitary to exogenous GnRH was accentuated during the time of maximal tonic LH/FSH suppression. ORG 30850 is a potent long-acting GnRH antagonist. Furthermore, the present in vivo demonstration of heightened pituitary responsiveness to exogenous GnRH emphasizes the divergent mechanisms of action of GnRH antagonists and GnRH agonists.

L2 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:693123 CAPLUS
DOCUMENT NUMBER: 121:293123
TITLE: Seven-day administration of the gonadotropin-releasing hormone antagonist Cetrorelix in normal cycling women
AUTHOR(S): Sommer, Lieselotte; Zanger, Kerstin; Dyong, Thomas; Dorn, Christoph; Luckhaus, Johannes; Diedrich, Klaus; Klingmuller, Dietrich
CORPORATE SOURCE: Dep. Clinical Biochemistry Clinical Hosp. Gynecology Obstretics, Univ. Bonn, Germany
SOURCE: European Journal of Endocrinology (1994), 131(3), 280-5
CODEN: EJOEEP; ISSN: 0804-4643
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In contrast to gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists do not show any stimulatory effect on the pituitary but their clin. usage was precluded by severe side effects and high dose requirements. The authors report here on a 7-day treatment using the

potent GnRH antagonist Cetrorelix ([Ac-D-Nal(2)1,D-Phe(4Cl)2,D-Pal(3)3,D-Cit6,D-Ala10]GnRH) on five women 23-33 yr old. All women were ovulatory and were studied during three consecutive cycles; a control cycle, a treatment cycle and a post-treatment control cycle. Throughout the control cycles blood samples were obtained daily during cycle days 8-18 and on days 21 and 23 during the remainder of the control cycles. On the eighth day of the treatment cycle women were hospitalized at 07.00 h for 26 h. Repeated blood samples were drawn at 15-min intervals during the entire period. Subjects received 3 mg of Cetrorelix s.c. for the first time at 09.00 h on the eighth day of the cycle and daily at 08.00 h for the following 6 days. Blood samples were obtained daily over a period of 25 days and every third day throughout the remainder of the treatment cycle. Twenty-four hours after the first application of Cetrorelix, LH and estradiol were in the subnormal range and remained subnormal until the end of medication. The suppressive effect of Cetrorelix compared to pretreatment values lasted at least 6 days for LH and FSH and 11 days after the last Cetrorelix compared to pretreatment values lasted at least 6 days for LH and FSH and 11 days after the last Cetrorelix injection for estradiol. An LH surge followed by postovulatory progesterone values was found 22.6 days after the last injection. During application of the GnRH antagonist, LH was reduced to 16.1%, FSH to 58.7% and estradiol to 17.9% compared to the individual pretreatment values. The consecutive cycle after completion of treatment was comparable to the length of the pretreatment cycle. No serious side effects were observed In summary, the results of this study give evidence of the effectiveness and safety of this new GnRH antagonist used in low dosages for possible therapeutic application in sex-hormone-dependent diseases in women.

L2 ANSWER 17 OF 24 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 93286163 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8509436
TITLE: Effects of the luteinizing-hormone-releasing hormone (LHRH) antagonist ramorelix (hoe013) and the LHRH agonist buserelin on dimethylbenz[]anthracene-induced mammary carcinoma: studies with slow-release formulations.
AUTHOR: Stoeckemann K; Sandow J
CORPORATE SOURCE: Hoechst AG, Pharma-Research, Frankfurt/Main, Germany.
SOURCE: Journal of cancer research and clinical oncology, (1993) Vol. 119, No. 8, pp. 457-62.
Journal code: 7902060. ISSN: 0171-5216.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 23 Jul 1993
Last Updated on STN: 6 Feb 1995
Entered Medline: 9 Jul 1993

AB Luteinizing-hormone-releasing hormone (LHRH) agonists and antagonists are antigonadotropic agents for reversible ovarian/testicular suppression in gynaecology and in oncology. Pituitary inhibition and suppression of the gonadal steroids can be maintained with continuous release rates from biodegradable implants or microparticles. The effects of curative and preventive treatment with slow-release formulations of the LHRH agonist buserelin (implants and microparticles) and the LHRH antagonist ramorelix (hoe013) (microparticles) on dimethylbenz[a]anthracene(DMBA)-induced mammary tumours in rats and the pharmacokinetics of these formulations are described. In addition, direct effects of the LHRH antagonist ramorelix on tumour growth were studied. The release rates of the implants

(polylactide-glycolide 75:25) and the microparticles (polylactide-glycolide 50:50) were calculated from urinary excretion of the peptides. The curative treatment started at the time of full tumour development (76 days after DMBA induction). A single buserelin implant injection (3.3 mg peptide) resulted in a dramatic tumour regression within 14 days, which was comparable to ovariectomy. It prevented tumour progression for 120 days. Previous studies in rats have shown that ramorelix microparticles (3.6 mg peptide) have a shorter duration of action (about 14 days) in suppression of gonadal function when compared to buserelin microparticles (3.6 mg peptide), where the suppression lasted for about 35 days. As expected, a single injection of ramorelix microparticles (3.6 mg peptide) inhibited tumour progression for only 14 days. This short action is due to a different release profile of the ramorelix microparticles and the different specific activities of peptides incorporated. In the preventive experiments animals were treated 17 days after DMBA induction before tumour development. Treatment with buserelin implants (3.3 mg peptide) every 56 days or with buserelin microparticles (3.6 mg peptide) every 28 days and the treatment with ramorelix microparticles (1.8 mg peptide) every 7 days prevented the development of tumours. Six weeks after the last injection of ramorelix microparticles a strong tumour progression was seen. There was a clear correlation between peptide release and tumour inhibition. The implants and the microparticles were well tolerated, no tissue reaction or side-effects of ramorelix were seen. Treatment of ovariectomized oestradiol-substituted DMBA-treated rats resulted in a marginal (not significant) inhibition in tumour development. LHRH antagonists in slow-release formulations (microparticles or implants) represent a new approach in treatment of hormone-dependent tumours because of the immediate onset of gonadal function and the increased drug efficacy due to the controlled release from biodegradable microparticles.

L2 ANSWER 18 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1993:248011 CAPLUS
DOCUMENT NUMBER: 118:248011
TITLE: Hormonal responses to the new potent GnRH antagonist Cetrorelix
AUTHOR(S): Klingmueller, D.; Schepke, M.; Enzweiler, C.; Bidlingmaier, F.
CORPORATE SOURCE: Dep. Clin. Biochem., Univ. Bonn, Bonn, Germany
SOURCE: Acta Endocrinologica (1993), 128(1), 15-18
CODEN: ACENA7; ISSN: 0001-5598
DOCUMENT TYPE: Journal
LANGUAGE: English
AB GnRH antagonists, unlike the GnRH agonists, immediately suppress gonadotropins and testosterone secretion without initial stimulatory effect. A single-dose study with the GnRH antagonist Cetrorelix (Ac-D-Nal(2)1, D-Phe(4Cl)2, D-Pal3, D-Cit6, D-Ala10) in 25 normal men is presented. The study involved 5 different dose groups (0.25, 0.5, 1.0, 1.5, or 3.0 mg) and subjects were observed over a 40 h period. Serum levels of LH, FSH, and testosterone decreased rapidly with a dose-related decline for testosterone of 25, 24, 41, 53, and 72%, resp., within the first 8 h of antagonist administration. All effects were reversible and no serious side effects were observed Thus, this GnRH antagonist is active in men even in small doses and could become a new therapeutic tool for sex hormone-dependent diseases. Cetrorelix seems to have the highest suppressive rate per mg peptide of all other antagonists from the literature. During the time of suppression after a dose of 3 mg there was an LH and testosterone peak in the early morning coinciding with the testosterone peak in untreated men. The GnRH antagonist seems to unmask the circadian rhythm of LH secretion.

L2 ANSWER 19 OF 24 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN DUPLICATE 6

ACCESSION NUMBER: 1992017444 EMBASE
TITLE: Effect of late follicular phase administration of antide on ovulation and inhibin secretion in macaques.
AUTHOR: Fraser H.M.; Lunn S.F.; Cowen G.M.; Smith K.B.; Conn P.M.
CORPORATE SOURCE: MRC Reproductive Biology Unit, Centre for Reproductive Biology, 37 Chalmers Street, Edinburgh EH9 3EW, United Kingdom
SOURCE: Contraception, (1991) Vol. 44, No. 6, pp. 667-676.
ISSN: 0010-7824 CODEN: CCPTAY
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 010 Obstetrics and Gynecology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 Mar 1992
Last Updated on STN: 20 Mar 1992

AB In previous studies, the LHRH antagonist detirelix, administered to stumptailed macaques during the menstrual cycle, was only partially effective in blocking pituitary-ovarian function when given during the late follicular phase. Since the antagonist was suppressive when administered during the early luteal phase, we investigated the ability of antide, a putative long-acting LHRH antagonist, to cause inhibition of the LH surge or luteal function when administered during the late follicular phase. Six animals with regular ovulatory cycles were treated on day 10 of the follicular phase with 1 mg/kg antide s.c. All animals demonstrated a continued rise in serum concentrations of estradiol which were followed by an LH surge beginning 2-5 days after antide injection and serum progesterone and inhibin secretion which indicated normal luteal function. In a second experiment, six animals were treated on day 10 of the follicular phase with 3 mg/kg antide s.c. In three animals, this caused a fall in serum concentrations of estradiol and the expected LH surge and rises in progesterone and inhibin secretion indicating ovulation failed to occur. In 2 animals, the LH surge was not prevented but the consequential rise in progesterone and inhibin was attenuated. In the remaining animal the cycle appeared unaffected. Pharmacokinetics of antide revealed an initial high release rate during the first 4 days (1 mg/kg) or 6 days (3 mg/kg) followed by a period of sustained release at a relatively low level. These results show that antide is partially effective in blocking ovulation at a high dose in the macaque and may result in an inadequate luteal phase, presumably as a result of its extended action.

L2 ANSWER 20 OF 24 MEDLINE on STN DUPLICATE 7

ACCESSION NUMBER: 92175455 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1794654
TITLE: Acute and subchronic toxicity studies with detirelix, a luteinizing hormone-releasing hormone antagonist, in the rat and monkey.
AUTHOR: Chester A E; Fairchild D G; Depass L R
CORPORATE SOURCE: Institute of Toxicologic Sciences, Syntex Research/R2-ITS, Palo Alto, California 94303.
SOURCE: Fundamental and applied toxicology : official journal of the Society of Toxicology, (1991 Oct) Vol. 17, No. 3, pp. 505-18.
Journal code: 8200838. ISSN: 0272-0590.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 24 Apr 1992
Last Updated on STN: 24 Apr 1992
Entered Medline: 6 Apr 1992

AB Acute (single dose), 2-week, and 3-month toxicology studies were conducted with detirelix, a luteinizing hormone-releasing hormone (LHRH) antagonist, in rats and cynomolgus monkeys. Acute studies were conducted by intravenous and subcutaneous injection. Subchronic studies were conducted by daily subcutaneous injection. Clinical signs after a single intravenous dose included lethargy, edema, cyanosis, pallor, and red ears in rats at greater than or equal to 0.3 mg/kg and lethargy and facial flushing in monkeys at greater than or equal to 0.5 mg/kg. In subchronic studies, detirelix at greater than or equal to 0.4 mg/kg/day (rats) and at greater than or equal to 0.2 mg/kg/day (monkeys) produced atrophy of the reproductive organs, inhibition of ovulation and spermatogenesis, decreased body weight gain in male rats and monkeys, and increased body weight gain in female rats. In the rat, morbidity and/or mortality occurred throughout the treatment phase at a subcutaneous dose of greater than or equal to 2.0 mg/kg/day. In both species, the time to recovery of normal reproductive organ morphology and function was directly related to dose. Exogenous testosterone decreased the severity of reproductive and body weight effects in male rats. In conclusion, the acute effects of detirelix were consistent with peripheral vasodilation. Subchronic effects were associated with inhibition of pituitary gonadotropic and gonadal hormone secretion.

L2 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1990:565566 CAPLUS
DOCUMENT NUMBER: 113:165566
TITLE: Single dose long-term suppression of testosterone secretion by a gonadotropin-releasing hormone antagonist (Antide) in male monkeys
AUTHOR(S): Edelstein, Michael C.; Gordon, Keith; Williams, Robert F.; Danforth, Douglas R.; Hodgen, Gary D.
CORPORATE SOURCE: Jones Inst. Reprod. Med., Eastern Virginia Med. Sch., Norfolk, VA, 23510, USA
SOURCE: Journal of Structural Biology (1990), 103(1), 209-14
CODEN: JSBIEM; ISSN: 1047-8477
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In adult male monkeys, at 3 mg/kg (s.c.), Antide blocked testosterone secretion for only a few days. However, when the dose of Antide was raised to 10 mg/kg, some of the males manifested testosterone inhibition lasting >60 days, whereas shorter durations of action were found in others. These preliminary findings increase interest in studying Antide as a potential male contraceptive agent, when combined with androgen replacement therapy, as well as for therapeutic applications in men with prostatic carcinoma. Importantly, Antide lacks the sometimes deleterious flare effect known to occur when LH-RH agonists are used to treat these patients.

L2 ANSWER 22 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1991:506335 CAPLUS
Correction of: 1990:565566
DOCUMENT NUMBER: 115:106335
Correction of: 113:165566
TITLE: Single dose long-term suppression of testosterone secretion by a gonadotropin-releasing hormone antagonist (Antide) in male monkeys
AUTHOR(S): Edelstein, Michael C.; Gordon, Keith; Williams, Robert

F.; Danforth, Douglas R.; Hodgen, Gary D.
CORPORATE SOURCE: Jones Inst. Reprod. Med., East. Virginia Med. Sch., Norfolk, VA, 23510, USA
SOURCE: Contraception (1990), 42(2), 209-14
CODEN: CCPTAY; ISSN: 0010-7824
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In adult male monkeys, at 3 mg/kg (s.c.), Antide blocked testosterone secretion for only a few days. However, when the dose of Antide was raised to 10 mg/kg, some of the males manifested testosterone inhibition lasting >60 days, whereas shorter durations of action were found in others. These preliminary findings increase interest in studying Antide as a potential male contraceptive agent, when combined with androgen replacement therapy, as well as for therapeutic applications in men with prostatic carcinoma. Importantly, Antide lacks the sometimes deleterious flare effect known to occur when LH-RH agonists are used to treat these patients.

L2 ANSWER 23 OF 24 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 90349493 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2201007
TITLE: Induction of chemical castration in male rats by a new long-acting LHRH-antagonist.
AUTHOR: Habenicht U F; Schneider M R; el Etreby M F
CORPORATE SOURCE: Research Laboratories of Schering AG, Berlin, Federal Republic of Germany.
SOURCE: The Prostate, (1990) Vol. 17, No. 1, pp. 69-83.
Journal code: 8101368. ISSN: 0270-4137.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199009
ENTRY DATE: Entered STN: 26 Oct 1990
Last Updated on STN: 26 Oct 1990
Entered Medline: 14 Sep 1990
AB LHRH-antagonists might represent a useful new type of androgen deprivation to treat prostatic cancer. In this context adult intact male rats were treated subcutaneously with different concentrations of the new LHRH-antagonist antide either once (1, 3, 6, 10, 15 mg/kg) or on 5 consecutive days (5 x 3 mg /kg). The effect on serum concentration of LH and testosterone and the effect on the weights of testes, prostate, and seminal vesicles was investigated after different periods of time (24 hours, 1, 2, 3, 5, and 8 weeks). Histological evaluation of the testes was also performed. A clear dose-dependent inhibitory effect on the above-mentioned parameters was observed. The most effective treatment schedule was the single application of 15 mg/kg resulting in castration-like inhibition of prostate weights and marked inhibition of spermatogenesis within 2 weeks, which was maintained 8 weeks after the injection. Serum LH and serum testosterone concentrations were below the detection limit of the assay within 2 weeks and showed first signs of recovery after 8 weeks. Histologically, no signs indicative of irreversible effects (testes) were observed. To summarize, the LHRH-antagonist antide was found to have a profound long-lasting inhibitory but reversible effect on the reproductive system of adult intact male rats. These data emphasize the suitability of this type of compound for the treatment of prostatic cancer.

L2 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1988:835 CAPLUS
DOCUMENT NUMBER: 108:835

TITLE: Characterizing pituitary response to a gonadotropin-releasing hormone (GnRH) antagonist in monkeys: tonic follicle-stimulating hormone/luteinizing hormone secretion versus acute GnRH challenge tests before, during, and after treatment

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AB Pituitary sensitivity to a gonadotropin-releasing hormone (GnRH) challenge test before, during, and after GnRH antagonist administration was compared in ovariectomized female monkeys (Macaca mulatta) receiving GnRH antagonist i.m. at increasing doses of 0.3, 1.0, and 3.0 mg/kg/day over 9 days. Three days before and 3 days after treatment, monkeys received vehicle alone. On experiment days 4, 7, 10, 13, and 16, 100 μg of GnRH was administered i.v. and blood drawn at 0 and 30 min. Before treatment, tonic FSH and LH levels were 248 and 178 ng/mL, resp.; after 0.3 mg/kg/day of GnRH antagonist, FSH and LH decreased to 30 and 41 ng/mL, resp. After treatment with either 1 mg/kg/day or 3 mg/kg/day of GnRH antagonist, both gonadotropins were undetectable in serum. Monkeys with lower initial levels of gonadotropins were suppressed by 48 h after GnRH antagonist, whereas those with higher tonic gonadotropins were suppressed 6 days later. Evidently, initial physiol. status is predictive of the rapidity of the suppression response induced by a GnRH antagonist, and, after achieving pituitary suppression, responsivity to an i.v. GnRH challenge test may be restored before normal tonic FSH/LH secretion is regained.

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